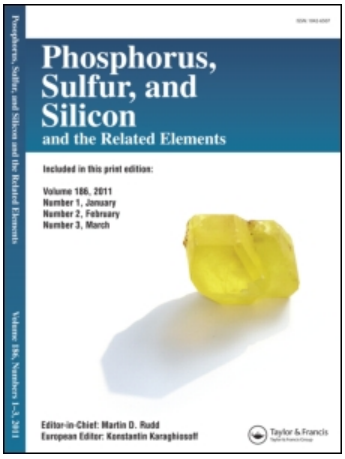

Phosphorus, Sulfur, and Silicon and the Related Elements

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Effect of Iodine on the Antimicrobial Activity of New Spiro and Isolated β-Lactam Thiazolidinone Derivatives

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Effect of Iodine on the Antimicrobial Activity of New Spiro and Isolated β-Lactam Thiazolidinone Derivatives

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*The reaction of 1,4-naphthoquinone with a mixture of urea and ethylcyanoacetate in ethanol containing a piperidine catalyst afforded compound **1**, which reacted with acetonitrile and steam of hydrogen chloride to yield compound 2, which readily condensed with different aromatic amine to give **3a–c**. Compound **3a–c** reacted with chloroacetyl chloride and/or mercaptoacetic acid to give spiro β-Lactam **4a–c**, and spiro thiazolidinone **5a–c** also isolated β-Lactam and thiazolidinone **7a–d** and **8a–d** prepared from a reaction of isolated schiff base **6a–d** with chloroacetyle chloride and mercaptoacetic acid. Compound **2** reacted with ethyl iodide to give compound **9**, which used to synthesis of new shiff bases **10a–c** and**13a–d**. The new schiff bases **10a–c** and **13a–d** reacted with chloroacetyl chloride or mercaptoacetic acid to give B-Lactams **11a–c** and **14a–d** and thiazolidinone derivatives **12a–c** and **15a–d**.*

Keywords Spiro B lactam, spiro thiazolidinone, shief base

INTRODUCTION

The explosive interest in β-Lactams and related derivatives stems from the fact that some monocyclic β-Lactams exhibit antibacterial activities. Some examples comprise of the naturally occuring monobactams and nocardicins.[1] Contrary to penicillins, cephalosporins, or nocardicins, monobactams were not produced by fungi or actinomycetes, but from bacteria, for example, *Bacillus pseudomonas*.[2] Nocardicins proved the relationship with cephalosporins and penicillins via the corresponding β-configuration at $C_{(3)}$, but they have no therapeutic significance. Synthetic oxamazins,[3–5] thiamazins,[6] and monosulfactams[7] showed some antibacterial activity, which raised again a major interest

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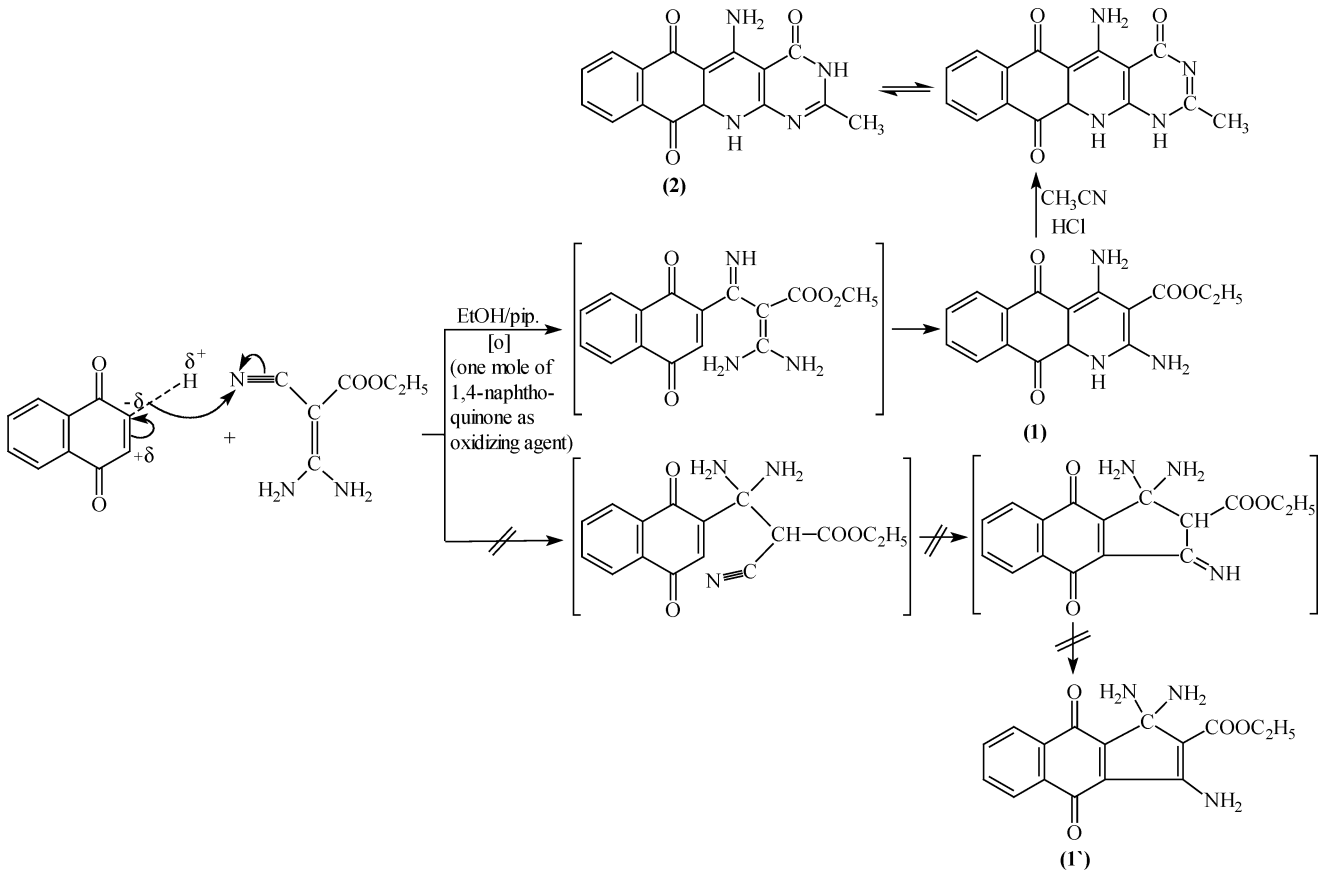
in the area of 2-azetidinone chemistry. Also thiazole derivatives such as pencillins, which have fused thiazolidine and β-Lactam rings, were known and used as potent antibiotics.[8]

RESULTS AND DISCUSSION

Our initial strategy in this research project for the synthesis of different structural formulas corresponding to the isolated, spiro, and fused systems depended upon the synthesis of the new fused 2,4-diamino-5, 10-dioxo-1,5,10,11-tetrahydrobenz[g]quinoline-3-ethyl carboxylate **1**, which was synthesized by a cycloaddition reaction of equimolecular ratios of the appropriate urea and ethylcyano acetate with 2 mole of 1,4-naphthoquinone (one mole used as an oxidizing agent), in ethanol containing piperidine as catalyst. At first our theortical conception of the obvious cycloaddition reaction led to the formation of compound **1**, but the expermental evidence that depends on the different types of analysis to the reaction product proved that the cycloaddition reaction leads to the formation of compound **1** through the electronic cyclization according to the suggested mechanism (Scheme 1 illustrates the formation of compound **1**).

The structure of the new synthesized compound **1** was confirmed by its elemental analysis and IR which revealed a carbonyl group of ester at 1745 cm^{-1} and ^1H NMR spectra, which revealed the presence of NH group at δ 11.02, NH_2 group at δ 6.82, NH_2 group at δ 4.53, a triplet at δ 1.23 assigned for methyl group, and quartet at δ 3.55 for CH_2 group. The mass spectrum showed the molecular ion peak (M^+, $C_{16}H_{15}O_4N_3$) at mz 313. The inteligible bases of ^1H NMR led us to descide that the isolable structural formula produced from the reaction of the appropriate urea and malononitrile with 1,4-naphthoquinone is the structural formula of compound **1** because of the appearance of the signal at δ 3.21 as a result of the fussion of 1,4-naphthoquinone with the unsaturated substituted piperidine ring.

Compound **2** was prepared by the reaction of compound **1** and acetonitrile with a stream of dry hydrogen chloride gas in the presence of dioxane for about 12 h, and the reaction mixture was heated on a water bath for 2 h after passing hydrogen chloride gas. The structure of the new synthesized compound **2** was confirmed by its elemental analysis and IR spectra, which revealed a signal of the carbonyl group at 1680 cm^{-1} and ^1H NMR spectra, which revealed the presence of NH group at δ 10.56, NH_2 group at δ 6.81, singlet signal at 1.25 for the methyl group. The absence of the signals assigned for the ethyl group indicate the structure of compound **2**; the mass spectrum showed the molecular ion peak (M^+, $C_{16}H_{12}O_3N_4$) at m/z 308.



SCHEME 1

Compound **2** underwent a fussion reaction with ethyl iodide to give compound **9**. The structure of compound **9** was confirmed by their elemental analysis, IR, ^{1}H NMR spectra, and mass spectra (cf. Table I, II, and III).

It is very important to know that the formation of Schiff bases corresponding to the newly heterocyclic compounds is the cornerstone in the synthesis of the corresponding spiro and isolated β-Lactams and thiazolidinone compounds. The activity of the carbonyl group in position **4** and also the activity of the methyl group at C_2 render compound **2** to react with different aromatic amine and different nitroso compound to give new Schiff bases **3a–c** and **6a–d**. The structures of these newly synthesized Schiff bases **3a–c** and **6a–d** were confirmed by their elemental analysis, IR, ^{1}H NMR, and mass spectra (cf. Tables I, II, and III.) The activity of the azamethine center in compound **3a–c** is more avaliable than the activity of the NH group toward the addition process of chloroacetyl chloride, and this mentioned phenomena is due to the presence of the π electron, which makes the foundation of the δ positive and δ negative charge on the carbon and nitrogen atom, respectively, more easy than the presence of this phenomena on the NH group in which the bonding between nitrogen and hydrogen wheather strong according to the nature of this bonding which leads to decreasing of the mobility desire of the hydrogen atom of this NH group. Thus compound **3a–d** reacted with chloroacetyl chloride or mercaptoacetic acid to give spiro β-Lactams and spiro thiazolidinone compounds[9] 4a–c and 5a–c. The structures of these spiro compounds **4a–c** and **5a–c** were confirmed by their elemental analysis, IR, ^{1}H NMR and mass spectra (cf. Tables I, II, III). The formation of spiro azitidine derivatives **4a–c** was suggested to proceed according to the following mechanisms (Scheme 2).

It is reported that β-Lactams play a vital role in medicinal chemistry as a key intermediate for the synthesis of penicillin, cephalosporins, and their analogs. On the other hand, thiazolidinones derivatives are used in biological activities such as bactericidal, pesticidal, and fungicidals, insecticidal activities.[10,11] Thus the activity of azamethine center in compound **6a–d** renders it avaliable to react with chloroacetyl chloride and/or mercaptoacetic acid to give new isolated β-Lactams and thiazolidinone compounds **7a–d** and 8a–d. The structures of compounds **7a–d** and **8a–d** were confirmed by their elemental analysis, IR, ^{1}H NMR and mass spectra [cf. Tables 1,2,3].

The application of heterocyclic compounds in various aspects is beyond estimation, and there is always continuous need for the discovery of new heterocyclic compounds, which are used in industrial and various biological fields. Thus we used the new compound **9** in the synthesis of spiro and isolated β-lactams and thiazolidinone compounds. Compound

TABLE I

Compound No.	Yield %	M.P.	Crystal solvent	Mol. formula	(Mol. Wt)	MS
1	75	>300	DMF	$C_{16}H_{15}O_4N_3$	(313.31)	313
2	65	>300	DMF	$C_{16}H_{12}O_3N_4$	(308.30)	308
3a	63	>300	DMF	$C_{22}H_{17}O_2N_5$	(383.41)	383
3b	60	>300	DMF	$C_{22}H_{17}O_3N_5$	(399.41)	399
3c	66	>300	DMF	$C_{22}H_{16}O_4N_5$	(414.40)	414
4a	70	>300	DMF	$C_{24}H_{18}O_3N_5Cl$	(459.90)	459
4b	69	>300	DMF	$C_{24}H_{18}O_4N_5Cl$	(475.90)	475
4c	73	>300	DMF	$C_{24}H_{17}O_5N_5Cl$	(490.89)	490
5a	75	>300	DMF	$C_{24}H_{19}O_3N_5S$	(457.51)	457
5b	72	>300	DMF	$C_{24}H_{19}O_4N_5S$	(473.51)	473
5c	74	>300	DMF	$C_{24}H_{18}O_5N_5S$	(488.50)	488
6a	67	>300	DMF	$C_{26}H_{17}O_4N_5$	(463.37)	463
6b	68	>300	DMF	$C_{26}H_{17}O_4N_5$	(463.37)	463
6c	70	>300	DMF	$C_{22}H_{15}O_4N_5$	(413.39)	413
6d	66	>300	DMF	$C_{24}H_{20}O_3N_6$	(440.46)	440
7a	69	>300	DMF	$C_{28}H_{18}O_5N_5Cl$	(539.94)	539
7b	68	>300	DMF	$C_{24}H_{18}O_5N_5Cl$	(539.94)	539
7c	65	>300	DMF	$C_{24}H_{16}O_5N_5Cl$	(489.88)	489
7d	77	>300	DMF	$C_{26}H_{21}O_4N_6Cl$	(516.87)	516
8a	76	>300	DMF	$C_{28}H_{19}O_5N_5S$	(537.55)	537
8b	74	>300	DMF	$C_{28}H_{19}O_5N_5S$	(537.55)	537
8c	73	>300	DMF	$C_{24}H_{17}O_5N_5S$	(487.49)	487
8d	72	>300	DMF	$C_{26}H_{22}O_4N_6S$	(514.56)	514
9	75	>300	DMF	$C_{18}H_{17}O_3N_4I$	(464.26)	464
10a	72	>300	DMF	$C_{24}H_{32}O_2N_5I$	(549.45)	549
10b	73	>300	DMF	$C_{24}H_{32}O_3N_5I$	(565.45)	565
10c	70	>300	DMF	$C_{24}H_{31}O_4N_5I$	(580.44)	580
11a	70	>300	DMF	$C_{26}H_{23}O_3N_5ClI$	(615.86)	615
11b	71	>300	DMF	$C_{26}H_{23}O_4N_5ClI$	(631.86)	631
11c	73	>300	DMF	$C_{26}H_{22}O_5N_5ClI$	(646.85)	646
12a	69	>300	DMF	$C_{26}H_{24}O_3N_5SI$	(613.47)	613
12b	70	>300	DMF	$C_{26}H_{24}O_4N_5SI$	(629.47)	629
12c	72	>300	DMF	$C_{26}H_{23}O_5N_5SI$	(644.46)	644
13a	73	>300	DMF	$C_{28}H_{22}O_4N_5I$	(619.41)	619
13b	71	>300	DMF	$C_{28}H_{22}O_4N_5I$	(619.41)	619
13c	69	>300	DMF	$C_{24}H_{20}O_4N_5I$	(569.35)	569
13d	68	>300	DMF	$C_{26}H_{25}O_3N_6I$	(596.42)	596
14a	70	>300	DMF	$C_{30}H_{23}O_5N_5ClI$	(695.90)	695
14b	72	>300	DMF	$C_{30}H_{23}O_5N_5ClI$	(695.90)	695
14c	69	>300	DMF	$C_{26}H_{21}O_5N_5ClI$	(645.84)	645
14d	71	>300	DMF	$C_{28}H_{26}O_4N_6ClI$	(672.91)	672
15a	69	>300	DMF	$C_{30}H_{24}O_5N_5SI$	(693.51)	693
15b	67	>300	DMF	$C_{30}H_{24}O_5N_5SI$	(693.51)	693
15c	70	>300	DMF	$C_{26}H_{22}O_5N_5SI$	(743.45)	743
15d	68	>300	DMF	$C_{28}H_{27}O_4N_6SI$	(670.52)	670

TABLE II

Compound No.	^{1}H NMR (DMSO) ppm
1	δ1.23(t, CH_3), δ 3.55(q, CH_2), δ 4.53(s, NH_2), 6.82(s, NH_2), δ 11.02(s, NH), 8.1–7.02(m, 5H aromatic hydrogen)
2	δ1.25(s, CH_3), δ 6.81(s, NH_2), δ 10.56(brs, NH), 8.01–7.1(m,7H aromatic protons)
3a	δ1.24(s, CH_3), δ 6.79(s, NH_2), δ 10.55(brs, NH), 8.1–7.01(m, 11H aromatic protons)
3b	δ1.259(s, CH_3), δ 6.77(s, NH_2), δ 10.56(brs, NH), 8.1–7.01(m, 11H aromatic protons)
3c	δ1.26(s, CH_3), δ 6.78(s, NH_2), δ 10.57(brs, NH), 8.1–7.01(m, 10H aromatic protons)
4a	δ1.24(s, CH_3), δ 6.75(s, NH_2), δ 10.43(brs, NH), 8.1–7.01(m, 12H aromatic protons)
4b	δ1.23(s, CH_3), δ 6.73(s, NH_2), δ 10.44(brs, NH), 8.1–7.01(m, 12H aromatic protons)
4c	δ1.24(s, CH_3), δ 6.74(s, NH_2), δ 10.45(brs, NH), 8.1–7.01(m, 11H aromatic protons)
5a	δ1.24(s, CH_3), 2.5(s, CH_2 protons), δ 6.76(s, NH_2), δ 10.55(brs, NH), 8.1–7.01(m, 10H aromatic protons)
5b	δ1.23(s, CH_3), 2.5(s, CH_2 protons), δ 6.75(s, NH_2), 10.54(brs, NH), 8.1–7.01(m, 10H aromatic protons)
5c	δ1.24(s, CH_3), 2.5(s, CH_2 protons), δ 6.75(s, NH), 10.54(brs, NH), 8.1–7.01(m, 9H aromatic protons)
6a	δ6.75(s, NH_2), δ 10.25(brs, NH), δ 8.1–7.01(m, 14H aromatic protons)
6b	δ6.73(s, NH_2), δ 10.26(brs, NH), 8.1–7.01(m, 14H aromatic protons)
6c	δ6.69(s, NH_2), δ 10.27(brs, NH), 8.1–7.01(m, 12H aromatic protons)
6d	δ1.25(ds, $2CH_3$), δ 6.66(s, NH_2), δ 10.26(brs, NH), 8.1–7.01(m, 11H aromatic protons).
7a	δ6.65(s, NH_2), δ 10.23(brs, NH), 8.1–7.01(m, 15H aromatic protons)
7b	δ6.67(s, NH_2), δ 10.24(brs, NH), 8.1–7.01(m, 15H aromatic protons)
7c	δ6.66(s, NH_2), 10.25(brs, NH), 8.1–7.01(m, 13H aromatic protons)
7d	δ1.23(ds, $2CH_3$), δ 6.65(s, NH_2), 10.25(brs, NH), 8.1–7.01(m, 15H aromatic protons)
8a	δ2.5(s, CH_2 of thiazolidinone), δ 6.6(s, NH_2), δ 10.26(brs, NH), 8.1–7.01(m, 14H aromatic protons)
8b	δ2.5(s, CH_2 of thiazolidinone), δ 6.65(s, NH_2), δ 10.25(brs, NH), 8.1–7.01(m, 14H aromatic protons)
8c	δ2.5(s, CH_2 of thiazolidinone), δ 6.64(s, NH_2), δ 10.23(brs, NH), 8.1–7.01(m, 12H aromatic protons)
8d	δ1.23(ds, $2CH_3$), δ 2.5(s, CH_2 of thiazolidinone), δ 6.66(s, NH2), 10.25(brs, NH), 8.1–7.01(m, 11 aromatic protons)
9	δ1.1(t, CH_3), δ 1.25(s, CH_3), δ 3.35(q, CH_2), δ 6.67(s, NH_2), δ 10.35(brs, NH), 8.1–7.01(m, 6H aromatic protons)
10a	δ1.12(t, CH_3), δ 1.24(s, CH_3), δ 3.36(q, CH_2), δ 6.65(s, NH_2), δ 10.36(brs, NH), 8.1–7.01(m, 21 aromatic protons)
10b	δ1.11(t, CH_3), δ 1.23(s, CH_3), δ 3.35(q, CH_2), δ 6.66(s, NH_2), δ 10.35(brs, NH), 8.1–7.01(m, 21H aromatic protons)
10c	δ1.12(t, CH_3), δ 1.24(s, CH_3), δ 3.37(q, CH_2), δ 6.67(s, NH_2), 10.34(brs, NH), 8.1–7.01(m, 20H aromatic protons)

(Continued on next page)

TABLE II (Continued)

Compound No.	^{1}H NMR (DMSO) ppm
11a	δ1.11(t, CH_3), δ 1.23(s, CH_3), δ 3.36(q, CH_2), δ 6.68(s, NH_2), 10.36(brs, NH), 8.1–7.01(m, 12H aromatic protons)
11b	δ1.12(t, CH_3), δ 1.24(s, CH_3), 3.35(q, CH_2), δ 6.67(s, NH_2), 10.35(brs, NH), 8.1–7.01(m, 12H aromatic protons)
11c	δ1.11(t, CH_3), δ 1.23(s, CH_3), 3.35(q, CH_2), δ 6.68(s, NH_2), 10.35(brs, NH), 8.1–7.01(m, 13H aromatic protons)
12a	δ1.12(t, CH_3), δ 1.23(s, CH_3), δ 2.5(s, CH_2 of thiazolidinone), δ 3.35(q, CH_2), δ 6.65(s, NH_2), 10.33(brs, NH), 8.1–7.01(m, 11H aromatic protons)
12b	δ1.1(t, CH_2), δ 1.23(s, CH_3), δ 2.5(s, CH_2 of thiazolidinone), δ 3.36(q, CH_2), δ 6.66(s, NH_2), 10.34(brs, NH), 8.1–7.01(m, 11H aromatic protons)
12c	δ1.12(t, CH_3), δ 1.22(s, CH_3), δ 2.5(s, CH_2 of thiazolidinone), δ 3.33(q, CH_2), δ 6.65(s, NH_2), 10.35(brs, NH), 8.1–7.01(m, 10H aromatic protons)
13a	δ1.12(t, CH_3), δ 3.35(q, CH_2), δ 6.66(s, NH_2), 10.36(brs, NH), 8.1–7.01(m, 14H aromatic protons)
13b	δ1.11(t, CH_3), δ 3.34(q, CH_2), δ 6.65(s, NH_2), 10.35(brs, NH), 8.1–7.01(m, 14H aromatic protons)
13c	δ1.12(t, CH_3), δ 3.35(q, CH_2), δ 6.67(s, NH_2), 10.36(brs, NH), 8.1–7.01(m, 12H aromatic protons)
13d	δ1.12(t, CH_3), δ 1.25(s, $2CH_3$), δ 3.36(q, CH_2), δ 6.66(s, NH_2), 10.35(brs, NH), 8.1–7.01(m, 17H aromatic protons)
14a	δ1.12(t, CH_3), δ 3.35(q, CH_2), δ 6.65(s, NH_2), 10.33(brs, NH), 8.1–7.01(m, 15H aromatic protons)
14b	δ1.11(t, CH_3), δ 3.36(q, CH_2), δ 6.66(s, NH_2), 10.35(brs, NH), 8.1–7.01(m, 15H aromatic protons)
14c	δ1.1(t, CH_3), δ 3.35(q, CH_2), δ 6.64(s, NH_2), 10.34(brs, NH), 8.1–7.01(m, 13H aromatic protons)
14d	δ1.12(t, CH_3), δ 1.23(s, $2CH_3$), δ 3.36(q, CH_2), δ 6.65(s, NH_2), 10.35(brs, NH), 8.1–7.01(m, 12H aromatic protons)
15a	δ1.12(t, CH_3), δ 2.5(s, CH_2 of thiazolidinone), δ 3.34(q, CH_2), δ 6.67(s, NH_2), 10.36(brs, NH), 8.1–7.01(m, 12H aromatic protons)
15b	δ1.11(t, CH_3), δ 2.5(s, CH_2 of thiazolidinone), δ 3.35(q, CH2), δ 6.66(s, NH_2), 10.33(brs, NH), 8.1–7.01(m, 12H aromatic protons)
15c	δ1.05(t, CH_3), δ (s, CH_2 of thiazolidinone), δ 3.36(q, CH_2), δ 6.64(s, NH_2), 10.34(brs, NH), 8.1–7.01(m, 14H aromatic protons)
15d	1.12(t, CH_3), 1.24(s, $2CH_3$), δ 2.5(s, CH_2 of thiazolidinone), δ 3.35(q, CH_2), δ 6.66(s, NH_2), 10.36(brs, NH), 8.1–7.01(m, 11H aromatic protons)

9 was prepared by the reaction of compound **2** with ethyl iodide, which was heated together under fussion for 1 h. The structure of compound **9** was confirmed by elemental analysis, IR spectra, and ^{1}H NMR which reaveled the presense of a singlet signal for the methyl group at δ 1.25, a quarted signal at 3.45 for CH_2, and a triplet signal at 1.02 for the

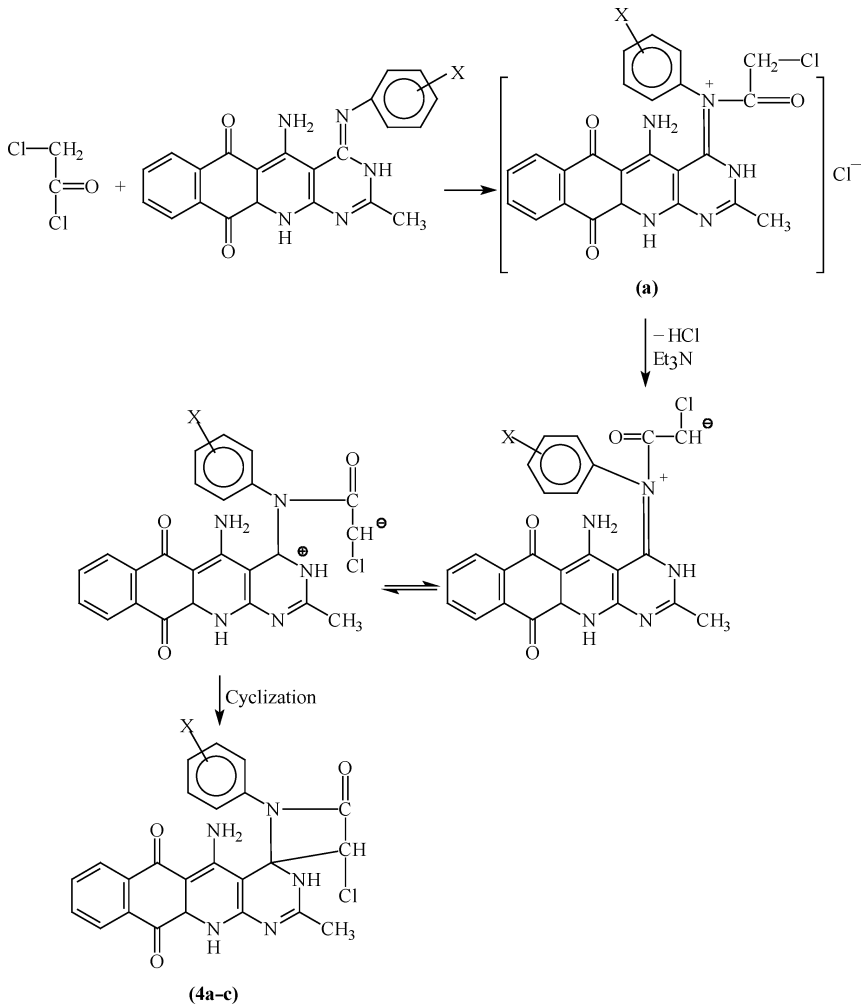
TABLE III

Compound No.	IR υ_{max}/cm^{-1}	(Calcd.) Found C	H	N	S	Cl
1	3400–3100(NH, NH_2), 1745 (C=O ester), 1645 (C=O)	(61.34)	(4.83)	(13.41)	—	—
		61.30	4.78	13.39	—	—
2	3400–3150(NH, NH_2), 1685(C=O), 1660(C=O)	(62.34)	(3.92)	(18.17)	—	—
		62.29	3.89	18.13	—	—
3a	3400–3100(NH, NH_2), 1665(C=O), 1585(C=N)	(68.92)	(4.47)	(18.27)	—	—
		68.88)	4.42	18.23	—	—
3b	3400–3100(NH, NH_2, OH), 1660(C=O), 1590(C=N)	(66.16)	(4.29)	(17.53)	—	—
		66.13	4.25	17.49	—	—
3c	3400–3100(NH, NH_2), 1650(C=O), 1580(C=N)	(63.77)	(3.89)	(16.90)	-	-
		63.73	3.86	16.86	—	—
4a	3400–3100(NH, NH_2), 1655(C=O)	(62.68)	(3.95)	(15.23)	—	(7.71)
		62.65	3.91	15.19	—	7.58
4b	3450–3100(NH, NH_2, OH), 1665(C=O)	(60.57)	(3.81)	(14.72)	—	(7.45)
		60.52	3.78	14.68	—	7.41
4c	3400–3100(NH, NH_2), 1660(C=O)	(58.72)	(3.49)	(14.27)	—	(7.22)
		58.69	3.45	14.23	—	7.19
5a	3400–3150(NH, NH_2), 1650(C=O)	(63.01)	(4.19)	(15.31)	(7.01)	—
		62.99	4.18	15.29	6.98	—
5b	3450–3100(NH, NH_2, OH), 1655(C=O)	(60.88)	(4.04)	(14.79)	(6.77)	—
		60.83	4.01	14.75	6.74	—
5c	3400–3150(NH, NH_2), 1650(C=O)	(59.01)	(3.71)	(14.34)	(6.56)	—
		58.98	3.68	13.99	6.52	—
6a	3450–3100(NH, NH_2, OH), 1670(C=O), 1595(C=N)	(67.38)	(3.70)	(15.11)	—	—
		67.34	3.67	15.07	—	—
6b	3450–3100(NH, NH_2, OH), 1675(C=O), 1585(C=N)	(67.38)	(3.70)	(15.11)	—	—
		67.35	3.65	15.05	—	—
6c	3450–3100(NH, NH_2, OH), 1660(C=O), 1590(C=N)	(63.92)	(3.66)	(16.94)	—	—
		63.88	3.62	16.90	—	—
6d	3450–3100(NH, NH_2), 1655(C=O), 1580(C=N)	(65.45)	(4.58)	(19.08)	—	—
		65.41	4.53	19.04	—	—
7a	3450–3100(NH, NH_2, OH), 1660(C=O)	(62.29)	(3.36)	(12.97)	—	(6.57)
		62.26	3.32	12.93	—	6.54
7b	3400–3100(NH2NH_2, OH), 1690–1660(C=O)	(62.29)	(3.36)	(12.97)	—	(6.57)
		62.25	3.31	12.92	—	6.52
7c	3400–3100(NH, NH_2, OH), 1717–1665(C=O)	(58.84)	(3.29)	(14.30)	—	(7.24)
		58.81	3.24	14.26	—	7.19
7d	3400–3100(NH, NH_2), 1718—1660(C=O)	(60.40)	(4.10)	(16.27)	—	6.86
		60.35	3.97	3.97	—	6.82
8a	3400–3100(NH, NH_2, OH), 1717–1655(C=O)	(62.56)	(3.56)	(13.03)	(5.94)	—
		62.51	3.53	12.99	5.90	—
8b	3450–3100(NH, NH_2, OH), 1720–1660(C=O)	(62.56)	(3.56)	(13.03)	(5.94)	—
		62.53	3.52	12.97	5.89	—

(Continued on next page)

TABLE III *(Continued)*

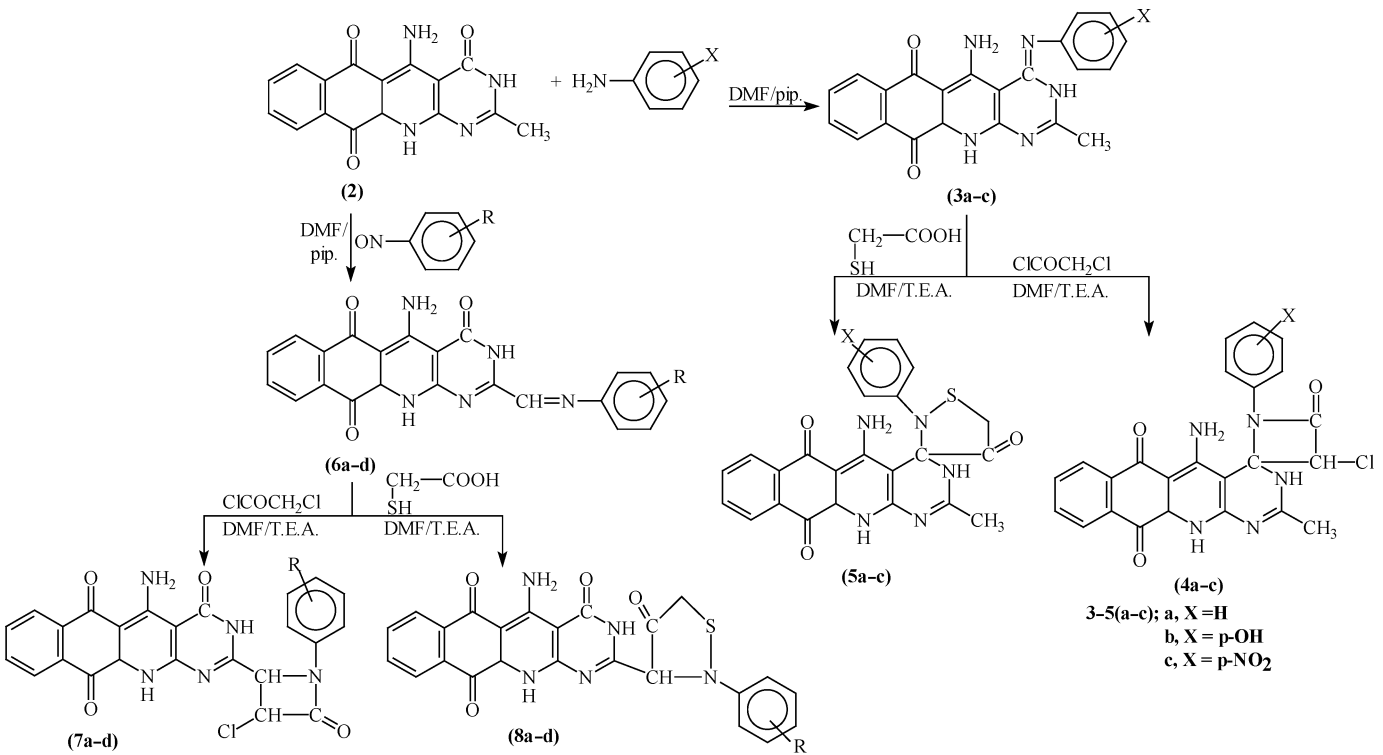
Compound No.	IR υ_{max}/cm^{-1}	(Calcd.) Found C	H	N	S	Cl
8c	3400–3100(NH, NH_2, OH),	(59.13)	(3.52)	(14.37)	(6.58)	—
	1717–1665(C=O)	59.09	3.49	14.33	6.54	—
8d	3400–3100(NH, NH_2),	(60.69)	(4.31)	(16.33)	(6.23)	–
	1720–1655(C=O)	60.64	4.28	16.29	6.19	—
9	3400–3100(NH, NH_2), 1680(C=O),	(46.57)	(3.69)	(12.07)	—	—
	1655(C=O)	46.53	3.66	12.03	—	—
10a	3450–3100(NH, NH_2), 1686(C=O),	(52.46)	(5.87)	(12.75)	—	—
	1590(C=N)	52.43	5.84	12.70	—	—
10b	3450–3100(NH, NH_2, OH), 1680(C=O),	(50.98)	(5.70)	(12.39)	—	—
	1580(C=N)	50.93	5.67	12.35	—	—
10c	3400–3100(NH, NH_2), 1685(C=O),	(49.66)	(5.38)	(12.07)	—	—
	1590(C=N)	49.62	5.35	12.03	—	—
11a	3450–3100(NH, NH_2),	(50.71)	(3.76)	(11.37)	—	(5.76)
	1725–1655(C=O)	50.68	3.72	11.34	—	5.73
11b	3450–3100(NH, NH_2, OH),	(49.42)	(3.67)	(11.08)	—	(5.61)
	1720–1660(C=O)	49.38	3.64	11.03	—	5.57
11c	3400–3100(NH, NH_2),	(48.28)	(3.43)	(10.83)	—	(5.48)
	1725—1650(C=O)	48.23	3.38	10.79	—	5.45
12a	3400–3100(NH, NH_2),	(50.91)	(3.94)	(11.42)	(5.23)	—
	1730–1660(C=O)	50.87	3.90	11.38	5.19	—
12b	3450–3100(NH, NH_2, OH),	(49.61)	(3.84)	(11.13)	(5.09)	—
	1725–1655(C=O)	49.58	3.81	11.90	5.04	—
12c	3400–3100(NH, NH_2),	(48.46)	(3.60)	(10.87)	(4.98)	—
	1720—1650(C=O)	48.42	3.55	10.83	4.92	—
13a	3450–3100(NH, NH_2, OH), 1675(C=O),	(54.30)	(3.58)	(11.31)	—	—
	1587(C=N)	54.27	3.54	11.28	—	—
13b	3450–3100(NH, NH_2, OH), 1665(C=O),	(54.30)	(3.58)	(11.31)	—	—
	1589(C=N)	54.26	3.52	11.26	—	—
13c	3450–3100(NH, NH_2, OH), 1670(C=O),	(50.63)	(3.54)	(12.30)	—	—
	1585(C=N)	50.60	3.49	12.27	—	—
13d	3400–3100(NH, NH_2), 1668(C=O),	(52.36)	(4.23)	(14.09)	—	—
	1590(C=N)	52.32	4.18	14.06	—	—
14a	3450–3100(NH, NH_2, OH),	(51.78)	(3.33)	(10.06)	—	(5.10)
	1717–1650(C=O)	51.73	3.29	10.03	—	4.98
14b	3450–3100(NH, NH_2, OH),	(51.78)	(3.33)	(10.06)	—	(5.10)
	1720–1655(C=O)	51.75	3.27	10.01	—	4.96
14c	34540–3100(NH, NH_2, OH),	(48.39)	(3.28)	(10.84)	—	(5.49)
	1725–1660(C=O)	48.35	3.23	10.80	—	5.46
14d	3400–3100(NH, NH_2),	(49.98)	(3.89)	(12.49)	—	(5.27)
	1720–1655(C=O)	49.92	3.84	12.45	—	5.23
15a	3450–3100(NH, NH_2, OH),	(51.96)	(3.49)	(10.10)	(4.62)	—
	1720–1666(C=O)	51.93	3.45	9.98	4.58)	—
15b	3450–3100(NH, NH_2, OH),	(51.96)	(3.49)	(10.10)	(4.62)	—
	1717–1655(C=O)	51.91	3.43	9.96	4.55	—
15c	3450–3100(NH, NH_2, OH),	(42.01)	(2.98)	(9.42)	(4.31)	—
	1717–1650(C=O)	41.99	2.94	9.38	4.27	—
15d	3400–3100(NH, NH_2), 1717–1660(CO)	(50.16)	(4.06)	(12.53)	(4.78)	—
		50.12	4.03	12.48	4.72	—



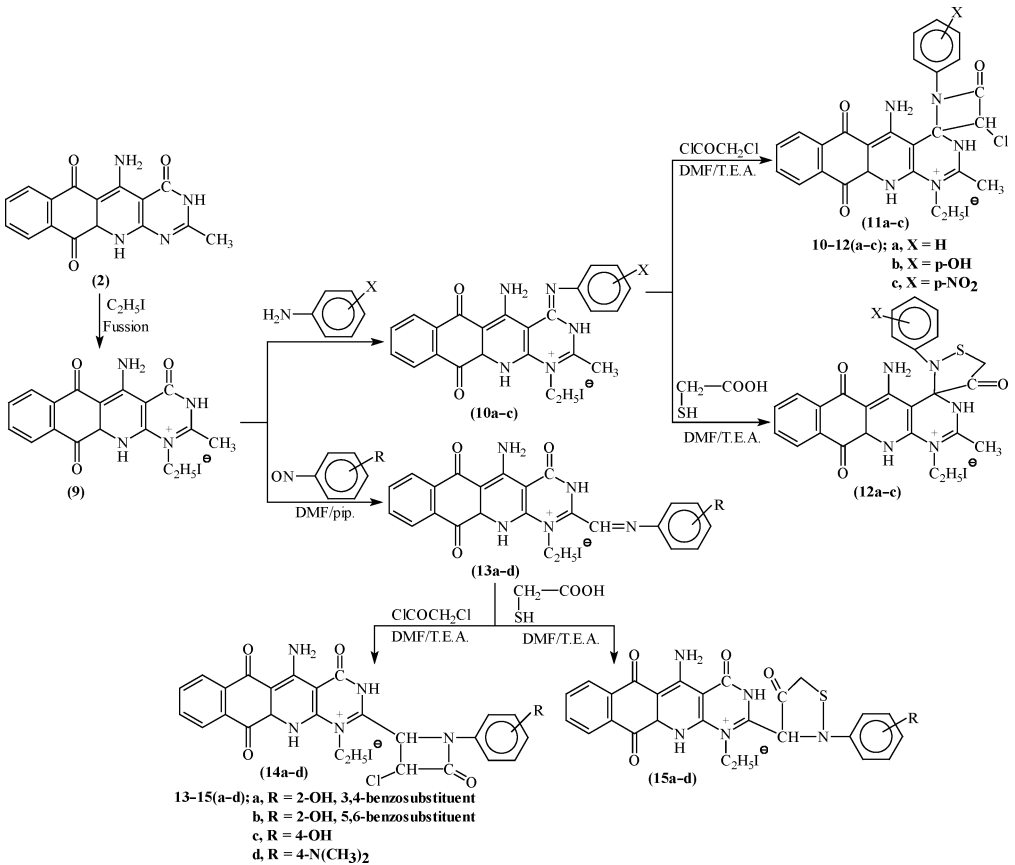
SCHEME 2

CH_3 group, and NH_2 group at δ 6.75. The mass spectrum showed the molecular ion peak (M^+, $C_{18}H_{17}O_3N_4I$) at m/z 464.

The activity of the carbonyl group in position **4** and the activity of the methyl group at C_2 rendered compound **9**, which contained iodine to react with different aromatic amine and different nitroso compounds to give new Schiff bases **10a–c** and **13a–d**. The structures of these newly synthesized Schiff bases compounds **10a–c** and **13a–d** were confirmed by their elemental analysis, IR, ^{1}H NMR, and mass spectra (cf. Tables I,



SCHEME 3



SCHEME 4

II, III). The activity of the azamethine center in compounds **10a–c** and **13a–d** is more avaliable than the activity of the NH group toward the addition process of chloroacetyl chloride, and this mentioned phenomena is due to the presence of the π electron, which makes the foundation of the δ positive and δ negative charge on the carbon and nitrogen atom, respectively, more easy than the presence of this phenomena on the NH group in which the bonding between nitrogen and hydrogen whether strong according the nature of this bonding, which leads to decreased mobility devise of the hydrogen atom of this NH group. Thus compound **10a–c** reacted with chloroacetylchloride or mercaptoacetic acid[9] to give spiro β-Lactams and spiro thiazolidinone compounds **11a–c** and **12a–c**. The structure of compounds **11a–c** and **12a–c** were confirmed by their elemental analysis, IR, ^{1}H NMR, and mass spectra (cf. Tables I, II, III). Also we synthesized isolated β-lactams and thiazolidinone compounds by the reaction of new Schiff bases **13a–d** with chloroacetyl chloride and/or mercaptoacetic acid to give **14a–d** and **15a–d**. The structures of these compounds were confirmed by their elemental analysis, IR, ^{1}H NMR, and mass spectra (cf. Tables I, II, III). We studied the effect of iodine on the antimicrobial activity of the synthesized compound. Thus the activity of eight synthesized compounds was examined in vito against three groups of microorganisms, including six strains of Gram positive bacteria, five strains of Gram negative bacteria, and three strains of fungi. The compounds were divided into two groups, four compounds with iodine in their structures and the other four compounds without iodine.

Several organo compounds are well authenticated to have antimicrobial activity versus many species of bacteria and fungi.[12–17] These authors pointed out that some of these compounds are useful in the treatment and/or control of human, animal, and plant diseases. The present investigation was carried out to investigate the antimicrobial activity of the eight synthesized compounds and shed new light on the effect of iodine on the antimicrobial activity of the eight synthesized compounds selected from the prepared compounds.

MATERIAL AND METHODS

Organisms

The microorganisms (No S. 1, 4, 6, 8, 9, 13, and 14) were obtained from the culture collection of the United State Department of Agriculture, Northern Regional Research Laboratory (Peoria, Illinois. USA), while others were obtained from the Botany Department microorganism collection and identified according to a key given in Bergy's Manual of

TABLE IV Antimicrobial Potentialities of the Tested Compounds Expressed as Size (mm) of the Inhibition Zone

	Compound									
Name	2	3a	4a	5a	9	10a	11a	12a	Ampicillin	Nystatin
1-*Bacillus subtilis NRS-744*	+	+	+	+	++	++	+++	+++	+	−
2-*Micrococcus luteus SW 712*	++	++	+	++	++	+++	+++	+++	+	−
3-*Bacillus megaterium SW 354*	++	++	+	+	+++	++	+++	+++	+	−
4-*Staphylococcus aureus B-767*	++	+	+	+	+++	++	+++	+++	+	−
5-*Streptomyces sp. SW 123*	++	−	+	+	++	++	++	+++	+	−
6-*Bacillus cereus ATCC-9634*	++	+	+	++	++	++	+++	+++	+	−
7-*Serratia Mar SW 98*	+	+	−	+	++	+	++	+++	+	−
8-*Pseudomonas aeruginosa ATCC-6NA10245*	−	+	−	+	+	++	++	+++	+	−
9-*Escherichia coli B-3704*	−	+	−	+	+	++	++	+++	+	−
10-*Salmonella sp. SW 476*	+	+	+	+	+	++	+++	+++	+	−
11-*Pseudomonas sp. SW 653*	−	+	+	+	+	++	+++	+++	+	−
12-*Sacharomyces cerevisiae SW 201*	+	+	−	+	++	+++	++	++	−	+
13-*Condida albicans IMRU3669*	+	+	+	−	++	+++	+++	++	−	+
14-*Aspergillus flouus S-C 43313*	+	−	+	+	++	++	+++	+++	−	+

Determinative Bacteriology.[18] Sacharomyces cerevisiae were identified as ascosporogenous.

Media

For the disc diffusion method, nutrient (NB) was used for cultivating the bacteria. It contained (g/L) the following: beef extract, 3; peptone, 5; and pH, 7.0. Czapek-Dox's agar medium was used for cultivating the fungi. It contained the following: (g/L) sucrose, 30.0; $NaNO_3$, 2.0; KCl, 0.5;

K_2HPO_4, 1.0; $MgSO_4$, $7H_2O$, 0.5; $FeSO_4$, 0.0004; agar, 20; and pH, 7.0–7.2. malt extractagar was used for cultivating the yeast. It contained the following: (g/L). malt extract, 20; peptone, 1; dextrose, 20; agar, 20; and pH, 7.0–7.2.

Preparation of Bacterial Suspensions

Suspensions of the microorganisms were prepared by suspending each bacteria in 5 mL sterile nutrient broth media, using a standard loop and then incubating the inoculated nutrient broth at 37°C for 2 h. One mL of each suspension was added to the center of the sensitivity testing plate. A sterile, dry cotton-wool swap was used to spread the inoculum on the media. The inocula were allowed to dry for a few minutes.

Preparation of Discs

Five compounds were tested as 200 μg/mL (W/V) solutions in sterile DMSO. Discs of 6-mm diameter of filter paper were placed in a petri dish (each one contained 10 discs) and then sterilized in a hot air oven at 180°C for 1 h. After cooling, 11 mL of the chemical solution was added onto each of the 10 discs to make a 20-μg concentration perone discs. The discs were dried in the incubator at 35–37°C, for 1 h, or dried over phosphorous pentaoxide (P_2O_5) in a dissector under vacuum, and then distributed on the inocula by sterile forceps.

Each disc should be pressed down on the medium and should not be moved once in place. The plates were incubated at 37°C overnight. The diameters of the clear zones of inhibition were measured to the nearest 0.5 mm, compared to DMSO, under the same standardized conditions. The data obtained are expressed as the size (mm) of inhibition zone. The diameter of the inhibition zones were high: (+ + +) (20–16 mm), moderate (++): (15–12 mm), slight (+): (11–1 mm), and no zone of inhibition (negative) (−).

Disc Diffusion Method for Three Tested Fungi

For the disc diffusion,[19] the discs of standard concentration (100 μg/disc) of each of the five tested compounds were appropriately placed on the surface of an agar plate freshly seeded with standard inoculum of young culture (3 days old). The plates were kept at 5°C for 1 h to allow diffusion of the compounds through the agar media. The plates of the fungal test organisms were maintained at 30°C for 4 days. At the end of the incubation period, the inhibition zones were measured.

Standard Antimicrobial and Antifungal

The preliminary antimicrobial[20] was recorded in comparison to standard antibacterial ampicillin (10 mg/ml) and antifungal nystatin (10 mg/ml) in distiled water.

RESULTS AND DISCUSSION

Many antimicrobial agents have been introduced into therapy;[21,22] however, the field still needs extensive efforts for the development of new antimicrobial agents of superior activity and less toxic side effects as well as to overcome the highly resistant strains of microorganisms. The data of the disc susceptibility tests for the compounds containing iodine, i.e., **9**, **10a**, **11a**,**12a**, clearly showed significant and potent antimicrobial activity (bactericidal and fungicidal) against the all-tested Gram positive bacteria and Gram negative bacteria and fungi. The compounds did not contain iodine, i.e., **2**, **3a**, **4a**, **5a** revealed weak susceptibility for the tested organisms compared with those of iodine, indicating that the presence of iodine in the compounds' structures enhanced the antimicrobial activity of the eight synthesized compounds. Compounds **11a** and **12a** exhibited the highest antimicrobial activity and were capable of inhibiting the growth of the all examined organisms.

EXPERIMENTAL SECTION

Melting points are uncorrected. IR spectra were measured as KBr pellets on a pye-unicam sp 1,000 spectrophotometer. ^{1}H NMR spectra were recorded in ($^2H_6$) dimethylsulfoxide at 200 MHz on a Varian Gemini NMR spectrometer using Mesi as an internal reference. Mass spectra were obtained on a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 eV. Elemental analysis were carried out at the Microanalytical Center of Cairo University.

Synthesis of 2,4-Diamino 5,10-dioxo-1,5,10,11-tetrahydrobenzo[g]quino-line-3-ethyl Carboxylate 1

A solution of the appropriate ethylcyano acetate and urea (0.01 mole), which was prepared in situ in ethanol (30 mL) containing (0.5 mL) piperidine, was treated with 1,4-naphthoquinone (0.02 mole, 1.58 g). The reaction mixture was heated under reflux for 10–12 h. The solvent was then evaporated under reduced pressure. Poured onto ice water acidified by HCl, the solid product that formed was collected by filtration and crystallized from DMF.

Synthesis of Compound 2

A stream of dry hydrogen chloride gas was passed through a mixture of compound 1 (3.13 gm, 10 mmol) and an appropriate acetonitrile (0.41 gm, 10 mmol) in dioxane (30 mL) for about 12 h. The reaction mixture was heated on a water bath for 2 h after passing hydrogen chloride gas. The reaction mixture was diluted with ice water and basified with 10% aq. ammonium hydroxide. The solid obtained as washed with water, dried, and crystallized from dimethyl formamide.

Synthesis of New Schiff Bases 3a–c and 6a–d

A solution of **2** (0.01 mole, 3.08 gm) in DMF (30 mL) was treated with different aromatic amines (0.01 mole) and/or different nitroso compounds (0.0l mole) in the presence of a catalytic amount of piperidine (0.5 mL). The reaction mixture was heated under reflux for 8–9 h (monitored by TLC). The solvent was then evaporated under reduced pressure, and the residue was treated with ice water acidified by HCl. The solid product was collected and crystallized from the proper solvent (cf. Table I).

Synthesis of Spiro β-Lactam 4a–c and Thiazolidinone 5a–c

A solution of **3a–c** (0.01 mole) in DMF (20 mL) was treated with chloroacetyl chloride or mercaptoacetic acid (0.01 mole) in the presence of (0.5 ml) triethylamine catalyst. The reaction mixture was heated under reflux for 15–17 h (monitored by TLC). The solvent was then evaporated under reduced pressure, and the residue was treated with ice water. The solid product was collected and crystallized from the proper solvent (cf. Table I).

Synthesis of Isolated β-Lactam 7a–d and Thiazolidinone 8a–d

A solution of **6a–d** (0.01 mole) in DMF (30 mL) was treated with chloroacetyl chloride or mercaptoacetic acid (0.01 mole), which was added drop by drop and stirred for 1 h in the presence of triethyl amine catalyst. The reaction mixture was heated under reflux for 18–20 h (monitored by TLC). The solvent was then evaporated under reduced pressure, and the residue was treated with ice water. The solid product was collected by filtration and crystallized from the proper solvent (cf. Table I).

Synthesis of Compound 9

A solution of ethyl Iodide (0.01 mole, 1.56 gm) was treated to compound 2 (0.01 mole, 3.08 gm) drop by drop and heated together by fussion for

1 h; the solid product was collected by ethanol and crystallized from the proper solvent (cf. Table I).

Synthesis of New Schiff Bases 10a–c and 13a–d

A solution of 9 (0.01 mole, 4.64 gm) in DMF (10 mL) and ethanol (20 mL) was treated with different aromatic amine (0.01 mole) and/or different nitroso compounds (0.01 mole) in the presence of a catalytic amount of piperidine (0.5 ml). The reaction mixture was heated under reflux for 7–8 h (monitored by TLC). The solvent was then evaporated under reduced pressure, and the residue was treated with ice water acidified by HCl. The solid product was collected by filtration and crystallized from the proper solvent (cf. Table I).

Synthesis of Spiro β-Lactam 11a–c and Thiazolidinone 12a–c

A solution of **10a–c** (0.01 mole) in DMF (30 mL) was treated with chloroacetyl chloride or mercaptoacetic acid (0.01 mole) in the presence of (0.5 ml) triethylamine catalyst. The reaction mixture was heated under reflux for 16–18 h (monitored by TLC). The solvent was then evaporated under reduced pressure, and the residue treated with ice water. The solid product was collected by filtration and crystallized from the proper solvent (cf. Table I).

Synthesis of Isolated β-Lactam 14a–d and Thiazolidinone 15a–d

A solution of **13a–d** (0.01 mole) in DMF (30 mL) was treated with chloroacetyl chloride or mercaptoacetic acid (0.01 mole), which was added drop by drop and stirred for 1 h in the presence of triethylamine catalyst. The reaction mixture was heated under reflux for 19–20 h (monitroed by TLC). The solvent was then evaporated under reduced pressure, and the residue was treated with ice water. The solid product was collected by filtration and crystallized from the proper solvent (cf. Table I).

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